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(54) Title: MESOPROGESTINS (PROGESTERONE RECEPTOR MODULATORS) AS A COMPONENT OF FEMALE CONTRACEPTIVES

(57) Abstract: The present invention relates to the use of mesoprogestins for the production of a pharmaceutical for female contraception, to a pharmaceutical preparation for female contraception and to a method of female contraception administering effective amounts of a mesoprogestin in a female desiring contraception. Optionally the mesoprogestin can be used in combination with an estrogen. Mesoprogestins are defined as compounds possessing both agonistic and antagonistic activities at the progesterone receptor (PR) in vivo. They stabilize the function of PR at an intermediate level of agonistic and antagonistic. Corresponding functional

Mesoprogestins (Progesterone Receptor Modulators) as a component of female contraceptives

The present invention relates to the field of contraception. More particularly it relates to the use of mesoprogestins for the production of a pharmaceutical for female contraception, to a pharmaceutical preparation for female contraception and to a method of female contraception administering effective amounts of a mesoprogestin to a female desiring contraception.

For female oral contraception different pharmaceutical preparations are available.

The most prevalent form of oral contraception is a pill that combines both an estrogen and a progestin, a so-called combined oral contraceptive preparation. Apparently, the progestin acts to block gonadotropin releases (inhibition of ovulation); the estrogen component provides endometrial control to diminish breakthrough bleeding.

Alternatively, there are contraceptive preparations that comprise progestin only. However, the progestin-only preparations (= progesterone-only pill = POP) have a more varied spectrum of side effects than do the combined preparations, especially more breakthrough bleeding. As a result, the combined preparations are the preferred oral contraceptives in use today (Sheth et al., Contraception, 25:243, (1982)).

Antiprogestins (also termed as „progesterone antagonits" or „antigestagens") are a class of compounds that block the progesterone receptor. For example, RU 486 (mifepristone) is a progesterone receptor antagonist. RU 486 binds to the progesterone receptor and produces a blockade of the binding of progesterone to ist receptor. When administered in the luteal phase of the menstrual cycle, RU 486 induces vaginal bleeding.

The prior art has demonstrated either inhibition of the ovulatory menstrual cycle or delayed endometrial maturation. It has been demonstrated in primate models that both a single injection of the antiprogestin RU 486 (5 mg/kg i.m.) in the late follicular phase or a once weekly oral RU 486 dose of 25 mg prevented ovulation (Collins et al., J. Clin. Endocrinol. Metab. 1986, 63:1270-1276; Danforth et al., Contraception 1989, 40:195-200).

Using various study protocols which differed in regimen and dose, it has been demonstrated by several groups of investigators that RU 486 inhibits ovulation in women as well (Shoupe et al., Am. J. Obstet. Gynecol. 1987, 157:1421-1426; Liu et al., J. Clin. Endocrinol. Metab. 1987, 65:1135-1140; Luukkainen et al., Fertil. Steril. 1988, 49:961-963).
An ovulation inhibiting activity has also been demonstrated for other progesteron antagonists than RU 486 (Zelinski-Wooten, M.B., Slayden, O.D., Chwalisz, K., Hess, D.L., Brenner, R.M., Stouffer, R.L .(1998a) Chronic treatment of female cycling rhesus monkeys with low-doses of the antiprogestin ZK 137 316: Establishment of a regimen that permits normal menstrual cyclicity. *Hum Reprod* 13: 259-267).

Consequently, several approaches for antiovulatory strategies to achieve contraception with progesterone antagonists have been suggested.

Also contraceptive approaches in which the RU 486 acts via implantation inhibition have been described.
In the so-called „LH+2" treatment (Swahn et al., „The luteal effect of RU 486 administration during the early luteal phase on bleeding pattern, hormonal parameters and endometrium", Human Reproduction 5, 4:402-408 (1990)) 2 days after occurrence of the LH peak (LH = Luteinizing Hormone) an ovulation-inhibiting dose of RU 486 is administered one time. The active compound is thus administered only after the time of ovulation in the luteal phase of the menstrual cycle (luteal contraception).

A contraception method using competitive progesterone antagonists is disclosed in WO 93/23020. Below their ovulation inhibiting dose and the abortive dose progesterone antagonist, preferably after oral administration, achieve contraception in females, by inhibition of implantation. The method does not adversely affect the female's menstrual cycle and is without risk of aborting a previous implanted fertilized egg or a fetus. The application of the progesterone antagonist occurs at least once in the follicular phase of the female's menstrual cycle (i.e. before ovulation). The preferred frequency of administration is daily or it follows in regular intervals of some days, e.g. weekly or with a distance of 3 or 4 days between the single administrations of active compound.

WO 94/18982 teaches a method of inhibiting fertilization of an oocyte which comprises administering a fertilizing inhibitory amount of an antiprogestin to an ovulatory mammal. The amount is insufficient either to prevent ovulation or to interfere with the regularity of the ovarian menstrual cycle of the mammal. The preferred frequency of administration is daily.

According to one aspect of the present invention mesoprogestins are used as a component for the production of a pharmaceutical for female contraception.
They can be used either as single pharmaceutically active principle in female contraceptives or they can be used together with an estrogen.

According to one aspect of the invention the mesoprogestins, either alone or in combination with estrogens, are used in a regular, cyclical administration regime. This shall mean that the mesoprogestins are administered in identical and repeating administration cycles as long as contraception is desired.
A cycle starts with the administration of a mesoprogestin or mesoprogestin / estrogen containing dosage unit followed daily by further dosage units thereof. Each cycle is completed by a period in which no active dosage units („pill-free" days) or in which placebos are administered.
Alternatively in case of mesoprogestin / estrogen administration the administration cycle can be completed by further administration of estrogen only containing dosage units.
A new application cycle starts on the first day after completion of the „pill free" or placebo phase, respectively or after the phase in which estrogen only containing dosage units have been administered.
In all cases day 1 in the first administration cycle is the first day of bleeding in the female's menstrual cycle in which the contraceptive treatment starts.

One embodiment of the mesoprogestin only administration provides for administering the mesoprogestin containing dosage units up to day 180 at the maximum. Under the continuos daily treatment (1 to 25 mg mesoprogestin/day) a reversible amenorrhoea is induced and maintained. The contraceptive effect is due to endometrial effects (endometrial suppression) of the mesoprogestin. Consequently the endometrium is not prepared for implantation of a fertilized egg. To achieve the contraceptive effect it is sufficient to administer the mesoprogestin in dosages to prevent nidation. The dose of the mesoprogestin can also be ovulation inhibiting but this is not essential to achieve the contraceptive effect and to induce and maintain amenorrhoea.
Preferably the mesoprogestin only administration takes place for 3 months at the maximum (this allows to check the contraceptive reliability of the method).
Compared to other contraceptive regimes which use progestins only the above described administration regime leads to a better bleeding behavior. Compared to the minipill

(progesterone only pill) and to subcutaneous implants loaded with a progestin (Norplant) less breakthrough bleedings are observed.
With the methods using a progesterone antagonist as disclosed in WO 93/23020 and WO 94/18982 the normal cycle was maintained.

A next embodiment of the mesoprogestin only administration takes place continuously for more than 3 months, for example, 1-3 years. Since a mesoprogestin suppresses endometrial growth and prevents endometrial vessel fragility it can be used chronically. In addition a condition of chronic but reversible amenorrhea is achieved.

A next embodiment of the mesoprogestin only administration provides for administering the mesoprogestin containing dosage units up to day 21, 22, 23, 24 or 25 either followed by a period of 7, 6, 5, 4 or 3 days during which no active compound is administered or followed by the administration of 7, 6, 5, 4 or 3 placebo pills so as to complete a 28 day long cycle. On the next day the next cycle starts with the administration of a mesoprogestin containing dosage unit, etc.
In this last mentioned administration regime the mesoprogestin acts like a progestin by blocking the ovulation and inducing amenorrhoea and triggering withdrawal bleeding. Breakthrough bleedings are not induced. The withdrawal bleeding is due to endometrial transformation induced by the mesoprogestin. Consequently, in this embodiment the mesoprogestin has to be administered, at least in the luteal phase of the female's menstrual cycle, in an ovulation-inhibiting dose.
A variant of the last mentioned embodiment (not yet claimed) is to administer dosage units containing mesoprogestin in an ovulation inhibiting dose exclusively during the luteal phase of the female's menstrual cycle (no administration in the follicular phase).

Amenorrhoea inducing doses of mesoprogestins can be determined by methods known to a person skilled in the art for example in clinical studies.
Generally the daily dose of the mesoprogestin will be in the range of 1 to 25 mg.

If an estrogen is administered in addition to the mesoprogestin both active components are administered from day 1 (see above) to day 21, 22, 23, 24 or 25 of the female's menstrual cycle either followed by a period of 7, 6, 5, 4 or 3 days during which no active compound is administered or followed by the administration of 7, 6, 5, 4 or 3 only estrogen containing dosage units or followed by the administration of 7, 6, 5, 4 or 3 placebo pills, respectively so

as to complete a 28 day long administration cycle. On the next day the next cycle starts with the administration of a mesoprogestin/estrogen containing dosage unit, etc.

The estrogen is used in a daily amount of 10 to 30 µg ethinyl estradiol or a bioequivalent amount thereof.

Mesoprogestins can be used sequentially with a progestin. In this contraceptive regimen the mesoprogestin component prevents breakthrough bleeding which is usually associated with chronic progestin treatment. The progestin component at a dose used in so called "mini pill regimen" is administered for a period of 30-180 days, whereas the mesoprogestin component is administered for a period of 1-30 days.
During mesoprogestin treatment menstrual bleeding may or may not occur. As a result of sequential progestin/mesoprogestin treatment the number of unscheduled bleeding is, however, markedly reduced.

The regular, cyclical administration regimes of a mesoprogestin, optionally in combination with an estrogen, are illustrated in detail in Figure 2.

The use of a mesoprogestin in a discontinuous, non-cyclical administration regime is the use as a so-called demand pill which has to be administered only around the time point of sexual intercourse for which contraception is desired. Preferably the administration is before sexual intercourse („medicinal condom"). For details c.f. WO 93/23020.

A further aspect of the invention refers to a pharmaceutical combination product (composition) containing a mesoprogestin together with an estrogen.

A further aspect of the invention refers to a pharmaceutical combination product (composition) containing a mesoprogestin together with a progestin.

Yet another aspect of the invention deals with pharmaceutical preparations for female contraception comprising daily dosage units of a mesoprogestin.
All the aspects of the pharmaceutical preparation according to the invention are apparent from claims 25 to 38.

As mesoprogestins i.a. compounds disclosed in DE 43 32 283 and in DE 43 32 284 are suitable for the purposes of the invention.

These aforementioned compounds, for instance J 867 [4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-oxim] and J 912 [4-[17β-Hydroxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-oxim] (both DE 43 32 283) and J 900 [4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-[O-(ethoxy)carbonyl]oxim], J 914 [4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-(O-acetyl)oxim] and J 956 [4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-[O-(ethylamino)carbonyl]oxim] (all DE 43 32 284) are described as compounds having strong antiprogestagenic and compared to RU 486 having markedly reduced antiglucocorticoid activity. Moreover these compounds are mentioned to have (indirect) antiestrogenic properties reflected by reduced uterine weights in cyclic guinea pigs.
These effects should promise the exertion of a particularly favorable influence on pathologically modified tissues in which estrogens stimulate growth (endometriotic focuses, myomas, etc.).
The disclosure of these applications does not pertain to the use of the new compounds for female contraception or to pharmaceutical preparations for this purpose.
Also, a progestagenic activity of the compounds which is advantageous for the herein claimed indication contraception is not mentioned in these applications at all.
Further, the mentioned applications are silent about any active dose to be used to treat any of the therein mentioned conditions.

According to the invention mesoprogestins are defined as compounds possessing both agonistic and antagonistic activities at the progesterone receptor (PR) in vivo. As progestins and antiprogestins, mesoprogestins show high binding affinity to PR. However, mesoprogestins exhibit different pharmacodynamic properties compared to either progestins or antiprogestins. The presence of progesterone agonistic activity in mesoprogestins measured in commonly used biological tests in vivo represents the key property of this novel class of PRMs. This activity remains, however, below that of progesterone in the plateau of the dose response curve. Mesoprogestins fail to maintain pregnancy in ovariectomized pregnant rodents as mice and rats.

In the classical bioassay, the McPhail test, assessing progestagenic and antiprogestagenic effects in rabbits (Selye H., Textbook of Endocrinology, 1947, pp. 345-346), progesterone produces a maximum McPhail score of 4 (by definition). Treatment with a mesoprogestin in the absence of progesterone leads, however, to a McPhail score which is higher than that

under any dose of RU 486, i.e. above 0.5 - 1.0, preferentially 2.0 - 3.0, but to distinctly lower score than 4 at the plateau of the dose response curve at the clinically relevant doses for the claimed indications (i.e. 0.01 mg – 30 mg/rabbit).

The capacity of mesoprogestins to antagonize progesterone function is also tested in the McPhail test using a progesterone dose which induces a McPhail score ranging between 3 and 4. A mesoprogestin inhibits the effect of progesterone to a significant degree, but the maximum inhibition is below that which is inducible with RU 486 or other pure antiprogestins (e.g. onapristone).

The mesoprogestins stabilize, therefore, the function of PR at an intermediate activity level providing the rationale for the novel clinical applications in gynecological therapy. Corresponding functional states cannot be achieved with progestins or antiprogestins.

Pharmacological results demonstrating the utility of the mesoprogestins in the claimed indications

The PR antagonistic and agonistic properties of mesoprogestins were assessed in estrogen-primed rabbits in the McPhail test according to Selye (Textbook of Endocrinology, 1947, pp. 345-346).

A) Assessment of PR agonistic properties of mesoprogestins in rabbits (Figure 1 A)

The progestagenic activity of J867, J956, J1042 [4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-[O-(ethylthio)carbonyl]oxim (German Patent Application 198 09 845.6)] and RU 486 (dose range: 0.003-100 mg/rabbit) was evaluated in estradiol-primed juvenile rabbits after 4 days of subcutaneous (s.c.) treatment in the absence of progesterone). The progestagenic effect of the mesoprogestins was observed at doses equal to or higher that 0.03 mg/rabbit. Progesterone induced endometrial transformation at doses equal to or higher that 0.1 mg reaching a maximum effect at 1 mg/rabbit (approximately McPhail score 4). Neither mesoprogestin tested (J1042, J867, J956) reached the maximum effect of progesterone. J956 showed a biphasic response in this test with a maximum effect of McPhail score 1.5 at 0.3-1 mg/rabbit.

B) Assessment of PR antagonistic properties of mesoprogestins in rabbits (Figure 1B)

Similarly, the antiprogestagenic activity of J867, J956, J1042 and RU 486 (dose range: 0.001-100 mg/rabbit) was evaluated in estradiol-primed juvenile rabbits after 4 days of subcutaneous (s.c.) treatment in the presence of progesterone (1 mg/rabbit s.c.). The first antiprogestagenic effect of the mesoprogestins and RU 486 was observed with a dose of 0.3-1 mg mg/rabbit (McPhail index 0 = no transformation; 4 = complete transformation). The antiprogestagenic activity of mesoprogestins at higher clinically relevant doses doses (i.e. 3-30 mg/rabbit) was lower that that of RU 486.

In the guinea pig model which allows a good prediction of the effects in humans with respect to the abortifacient activity (Elger W, Beier S., Chwalisz K, Fähnrich M, Hasan SH, Henderson D, Neef G, Rohde R (1986): Studies on the mechanism of action of progesterone antagonists. J Steroid Biochem 25: 835-845) the mesoprogestins J 867, J 912, J 956, J 1042 lead up to 100 mg/kg/day to a maximal abortion rate of 20%.

C) Evaluation of abortifacient effects

Physiological background:
The guinea pig is considered as relevant model of human gestation and parturition (Elger W, Fähnrich M, Beier S, Quing SS, Chwalisz K (1987). Endometrial and myometrial effects of progesterone antagonists in pregnant guinea pigs. *Am J Obstet Gynecol* 157: 1065-1074; Elger W, Neef G, Beier S, Fähnrich M, Gründel M, Heermann J, Malmendier A, Laurent D, Puri CP, Singh MM, Hasan SH, Becker H (1992). Evaluation of antifertility activities of antigestagens in animal model. In: Puri CP and Van Look PFA (eds), *Current Concepts in Fertility Regulation and Reproduction.* Wiley Eastern Limited, New Delhi, pp. 303-328; Elger W, Faehnrich M, Beier S, Qing SS, Chwalisz K (1986). Mechanism of action of progesterone antagonists in pregnant guinea pigs. *Contraception* 6: 47-62; Elger W, Chwalisz K, Faehnrich M, Hasan SH, Laurent D, Beier S, Ottow E, Neef G, Garfield RE (1990). Studies on labor-conditioning and labor-inducing effects of antiprogesterones in animal model. In: Garfield RE (eds), Norwell, pp. 153-175.) The mechanism of abortion of antiprogestins in this species is the initiation of labor and finally the expulsion of the conceptus. Abortifacient effects in the rat during very early pregnancy reflect inhibitory effects on nidation rather than initiation of uterine contractions. Studies in the rat model lead to "overestimation" of the potential of antiprogestins to terminate pregnancy in humans. Conversely, in the guinea pig model, irrespective of the antiprogestin doses, there were high rates of ongoing pregnancies

similar to the situation in humans (Elger et al., *Current Concepts in Fertility Regulation and Reproduction cited above)*. Furthermore, in both humans and guinea pigs, there is a strong synergism between antiprogestins and prostaglandins with respect the induction of labor (see the articles cited above and Elger W, Beier S (1983). Prostaglandine und Antigestagene für den Schwangerschaftsabbruch (Prostaglandins and antigestagens for pregnancy termination). *German Patent DE 3337450* 12; Van Look P, Bygdeman M (1989). Antiprogestational steroids: a new dimension in human fertility regulation. *Oxford reviews of reproductive medicine* 11: 2-60).

Assessment of labor inducing activity: Figure 3.

Pregnant guinea pigs were treated on days 43 and 44 of pregnancy and observed until day 50 of gestation. For the effects of various treatments see table 1 and figure 3. It is typical for this model that expulsions occur with a delay of several days after treatment. It can be seen that Mesoprogestins have a much reduced abortifacient activity compared to RU486. The following ranking of abortifacient activity was found: RU486>J956>J867, J912>J1042. The differences with respect to abortifacient activity seem qualitative ones. It is not possible to overcome the low abortifacient activity of a Mesoprogestin by the use of a higher dose.

Table 1: Studies of relative binding activity (RBA) and ED_{50} of abortifacient activity in pregnant rats and guinea pigs.

compound	RBA (%) #		abortifacient activity ED_{50} (mg/animal/day, s.c.)	
	PR[1]	GR[2]	rat[3]	guinea pig[4]
RU 486	506	685	0.98*	3.8
Onapristone	22	39	1.71*	ca 3
J867	302	78	0.65*	>100
J956	345	154	0.64*	20
J912	162	16	0.36	> 100
J1042	164	42	> 10	>> 100

by Kaufmann; [1]progesterone = 100%, [2]dexamethasone = 100%
[3]treatment days 5 – 7 of pregnancy, autopsy day 9, [4]treatment day 43 – 44 of pregnancy, autopsy day 50, *SAS, probit procedure.

The mesoprogestin is preferably selected for this invention from the group of the compounds J867, J912, J956, J1042.
Further preferred mesoprogestins are
4-[17β-Hydroxy-17α-(ethoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-oxim;
4-[17β-Methoxy-17α-(ethoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-oxim;
4-[17β-Hydroxy-17α-(chlormethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-oxim;
4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-(O-methyl)oxim (all DE 43 32 283)
and
4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-[O-(phenylamino)carbonyl]oxim;
4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-[propionyl]oxim;
4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11ß-yl]benzaldehyd-(1E)-[benzoyl]oxim (all DE 43 32 284).

The amount per daily dosage is in the range of 1 to 25 mg of mesoprogestin.

As estrogens, all estrogenically active compounds are suitable for the purposes of this invention.

- Estrogens that can be used within the scope of this invention are, for example, ethinylestradiol, 17β-estradiol as well as its esters such as estradiol-3-benzoate, estradiol-17-valerate, -cypionate, -undecylate, -enanthate and/or other estradiol esters (US-PS 2,611,773, US-PS 2,990,414, US-PS 2,054,271, US-PS 2,225,419 and US-PS 2,156,599) and conjugated estrogens.
- Estradiol-, ethinylestradiol- and estrone-3-sulfamates, for example estrone-N,N-dimethylsulfamate, estrone-N,N-diethylsulfamate, ethinylestradiol-3-N,N-dimethylsulfamate, ethinylestradiol-3-N,N-diethylsulfamate, ethinylestradiol-3-N,N-tetramethylenesulfamate, estrone sulfamate, estradiol-3-sulfamate, estradiol-3-N,N-dimethylsulfamate, estradiol-3-N,N-diethylsulfamate, ethinylestradiol-3-sulfamate, which all represent prodrugs for the corresponding 3-hydroxy compounds (W. Elger et al., in J.

Steroid Biochem. Molec. Biol., Vol. 55, No. 3/4, 395-403, 1995; DE 44 29 398 A1 and DE 44 29 397 A1), can also be used in the pharmaceutical agent according to the invention.

As progestins useful in the invention, all compounds are suitable that are suitable for use in oral contraceptives because of their progestin activity. An exemplary list of such compounds is found in B. Runnebaum et al., "Female Contraception: Update and Trends," Springer-Verlag, Berlin, 1988, pages 64-90, 109-121, 122-128 and 129-140. Preferred progestins within the scope of this invention are gestodene, progesterone, levonorgestrel, cyproterone acetate, chlormadinone acetate, drospirenone (dihydrospirorenone), norethisterone, norethisterone acetate, norgestimate, desogestrel or 3-ketodesogestrel. In the embodiment containing a progestin according to this invention, the progestin is present in a dosage form that is suitable for oral administration, namely as a tablet, coated tablet, capsule or pill. In this case, the formulation of the progestin is done in a way analogous to preparing progestins for hormonal contraception with use of the adjuvants that are commonly used for this purpose. A daily dosage unit of the progestin contains the latter at a dose of 0.6-6.0 mg of levonorgestrel, 2-20 mg of cyproterone acetate, 0.3-3.0 mg of gestodene or 0.2-2.0 mg of desogestrel or an amount of another progestin that is equivalent in action to these dosages.

Determining equivalent-action dose amounts of various progestins is done according to known methods; further details are found in, for example, the two articles "Probleme der Dosisfindung: Sexualhormone [Problems of Dose-Finding: Sex Hormones]"; F. Neumann et al. in "Arzneimittelforschung [Drug Research]" 27, 2a, 296-318 (1977) as well as "Aktuelle Entwicklungen in der hormonalen Kontrazeption [Current Developments in Hormonal Contraception]"; H. Kuhl in "Gynäkologe [Gynecologists]" 25: 201-240 (1992).

According to all embodiments, mesoprogestin can be present in dosage units that are intended for daily oral administration.

The estrogen can also be present in daily oral dosage units.

If the dosage units of the mesoprogestin are provided for administration over a period of 7 days, these dosage units can advantageously be present in the form of a dosage unit that can be administered once a week.

In such a dosage unit that is to be administered once a week, the mesoprogestin should preferably be prepared in a formulation that results in a delayed release of the active ingredient.

A delayed release of the mesoprogestin can be achieved, for example, by formulating the dosage unit that is to be administered orally as a composite tablet or by providing the dosage unit that is to be administered orally with a timed-disintegration coating, as is readily known to one skilled in the art.

By derivatization, for example by esterification of a free hydroxy group in an effective precursor, the mesoprogestin that is used for the production of the pharmaceutical agent according to the invention can also have a longer half-life than this precursor. As a result, a longer-lasting action is also achieved.

For the purposes of this invention, the formulation of the mesoprogestin and optionally the estrogen is done in a completely conventional manner, as is already known for the formulation of these compounds for their individual use as described for J867 in DE 43 32 283 and for estrogen therapy, for example Cyclo-Progynova.

In particular, reference is also made to the information that is contained in the mentioned prior art documents.

In addition to oral administration of the estrogen and the mesoprogestin, it is equally possible to administer one or both of the components transdermally, for example with a skin patch, which is best known for the administration of estrogen (Climara Patch).

In addition, administration can be done using an intrauterine release system (c.f. Mirena), but this variant is not preferred within the scope of this invention.

The administration of one or both components as a depot formulation is also possible.

Finally, all above-mentioned types of administration can be combined. For example, the estrogen can be administered transdermally with a skin patch, and the progesterone antagonist can be administered daily orally or one or more times as a depot formulation.

The estrogen is contained per daily dosage unit according to the invention in an amount of 10 to 30 µg of ethinylestradiol or a bioequivalent amount of another estrogen.

In the pharmaceutical agent according to the invention, the mesoprogestin is contained in each dosage unit preferably in an amount such that, when used over the intended length of time, it is sufficient for amenorrhea to occur.

In an preferred embodiment of the pharmaceutical agent according to the invention, the mesoprogestin is contained in each daily dosage unit in an amount that is equivalent to 1 to 25 mg of J 867.
The bioequivalent doses of a mesoprogestin can be assessed in the McPhail test.

The packaging that contains the pharmaceutical preparation according to the invention is prepared in such a way that, in addition to the one or two components mesoprogestin and estrogen in the respectively intended form of administration (orally in the form of pills, coated tablets, etc. in a blister pack, as may be appropriate for mesoprogestin and/or estrogen, or the estrogen as a skin patch and the mesoprogestin in the form of pills, coated tablets, etc. in a blister or in a capsule as a depot that is to be administered once), said packaging also contains instructions for the use of the pharmaceutical agent (package insert).

Claims:

1. Use of mesoprogestins as a component for the production of a pharmaceutical for female contraception.
2. Use of mesoprogestins according to claim 1 without any further pharmaceutically active compound being involved.
3. Use according to 1 or 2 of a mesoprogestin in a regular, cyclical administration regimen.
4. Use according to claim 3 characterized in that the administration of the mesoprogestin ensues from d1 up to maximally d180, d1 being counted as the first day of bleeding of the female's menstrual cycle.
5. Use according to claim 4 whereby the daily amount of the mesoprogestin is selected so as to induce and maintain amenorrhoea.
6. Use according to claim 5 characterized in that the administration of the mesoprogestin ensues from d1up to at least d21 and maximally d25, d1 being counted as the first day of bleeding of the female's menstrual cycle.
7. Use according to claim 6 whereby the daily amount is selected so as to achieve reversible amenorrhoe.
8. Use according to anyone of the preceding claims 1 to 7, wherein the mesoprogestin is J 867, J 912, J 956, J 1042.
9. Use according to anyone of the preceding claims 1 to 8 characterized in that the daily dose of the mesoprogestin is 1 to 25 mg.
10. Use according to claims 1 and 3 to 9 characterized in that as an additional component for production of the pharmaceutical an estrogen is used.
11. Use according to claim 10 characterized in that the additional component is ethinylestradiol, estradiol, estradiol ester or a 3-sulfamat of 17β-ethinylestradiol or 17β-estradiol.
12. Use according to claim 10 or 11 characterized in that the daily dose of the additional component estrogen is 10 to 30 µg ethinylestradiol or a bioequivalent amount of another estrogen.

13. Use according to anyone of preceding claims 1 to 12 characterized in that the pharmaceutical is formulated for oral administration.

14. Use according to anyone of preceding claims 1 to 12 characterized that the pharmaceutical is formulated as an intrauterine system.

15. Use according to claim 10, 11 or 12 characterized in that at least one of both, mesoprogestin and additional component estrogen, is formulated for oral administration.

16. Use according to claim 10, 11 or 12 characterized in that at least one of both, mesoprogestin and additional component estrogen, is formulated as an intrauterine system.

17. Use according to claim 2 in a discontinuous, non-cyclical administration regime.

18. Use according to claim 17 wherein the mesoprogestin containing pharmaceutical is administered on demand when contraception is desired actually for one occasion.

19. Use according to claim 18 wherein the administration is for a period of up to 4 days.

20. Use according to claim 19 wherein at least the first administration within the period of up to 4 days is before sexual intercourse for which contraception is desired.

21. Use according to claim 20 wherein the administration is once and before sexual intercourse.

22. Pharmaceutical composition containing a mesoprogestin and a estrogen.

23. Pharmaceutical composition according to claim 22 wherein the mesoprogestin is selected from the group of the compounds J 867, J 912, J 956, J 1042.

24. Pharmaceutical composition according to claim 22 wherein the estrogen is ethinylestradiol, estradiol, estradiol ester or a 3-sulfamat of 17β-ethinylestradiol or 17β-estradiol.

25. Pharmaceutical preparation for female contraception comprising daily dosage units of a mesoprogestin wherein dosage units for up to maximally 180 days are provided.

26. Pharmaceutical preparation according to claim 25 wherein consecutively to the mesoprogestin up to 7 placebos or measures to indicate up to 7 pill free days are provided.

27. Pharmaceutical preparation according to claim 26 wherein 21, 22, 23, 24 or 25 daily dosage units of the mesoprogestin and 7, 6, 5, 4 or 3 placebos or measures to indicate 7, 6, 5, 4 or 3 pill free days are provided.

28. Pharmaceutical preparation according to claims 26 or 27 wherein in addition to the mesoprogestin containing dosage units estrogen containing dosage units are provided.

29. Pharmaceutical preparation according to claim 28 wherein the mesoprogestin and the estrogen are contained in common dosage units.

30. Pharmaceutical preparation according to claim 28 wherein the mesoprogestin and the estrogen are contained in separate dosage units.

31. Pharmaceutical preparation comprising daily dosage units containing a mesoprogestin and a estrogen or a mixture of estrogens wherein these dosage units are provided for administration for 21, 22, 23, 24 or 25 days and wherein consequtively to these mesoprogestin/estrogen dosage units 7, 6, 5, 4 or 3 dosage units containing only estrogen or a mixture of estrogens are provided so that in total dosage units for administration for 28 days are provided.

32. Pharmaceutical preparation according to claim 31 wherein the mesoprogestin and the estrogen are contained in common dosage units.

33. Pharmaceutical preparation according to claim 31 wherein the mesoprogestin and the estrogen are contained in separate dosage units.

34. Pharmaceutical preparation according to anyone of preceding claims 25 to 33 wherein the mesoprogestin is J 867, J 912, J 956, J 1042.

35. Pharmaceutical preparation according to anyone of preceeding claims 28 to 34 wherein the estrogen is ethinylestradiol, estradiol, estradiol ester or a 3-sulfamat of 17β-ethinylestradiol or 17β-estradiol.

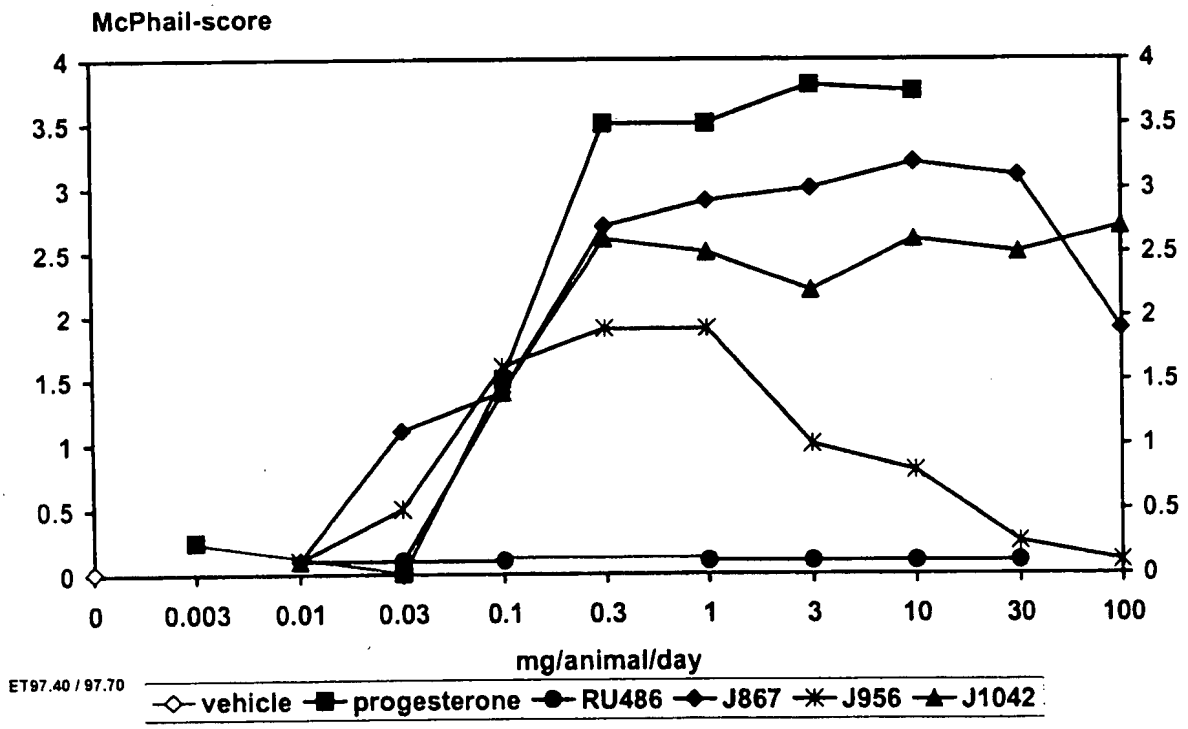
36. Pharmaceutical preparation according to anyone of preceding claims 25 to 35 wherein the daily dosage unit contains 1 to 25 mg of mesoprogestin.

37. Pharmaceutical preparation according to anyone of preceding claims 28 to 33, 35 and 36 wherein the daily dosage unit contains 10 to 30 µg ethinylestradiol or a bioequivalent amount of another estrogen.

38. Pharmaceutical preparation according to anyone of preceding claims 25 to 37 wherein the daily dosage unit contains an amenorrhoea inducing and amenorrhoea maintaining amount of a mesoprogestin.

Figures 1A and 1B

Progesterone-like (above, Fig. 1A) and progesterone antagonistic (below, Fig. 1B) effects of PR-modulators in the uterus of estrogen primed immature rabbits (McPhail test)



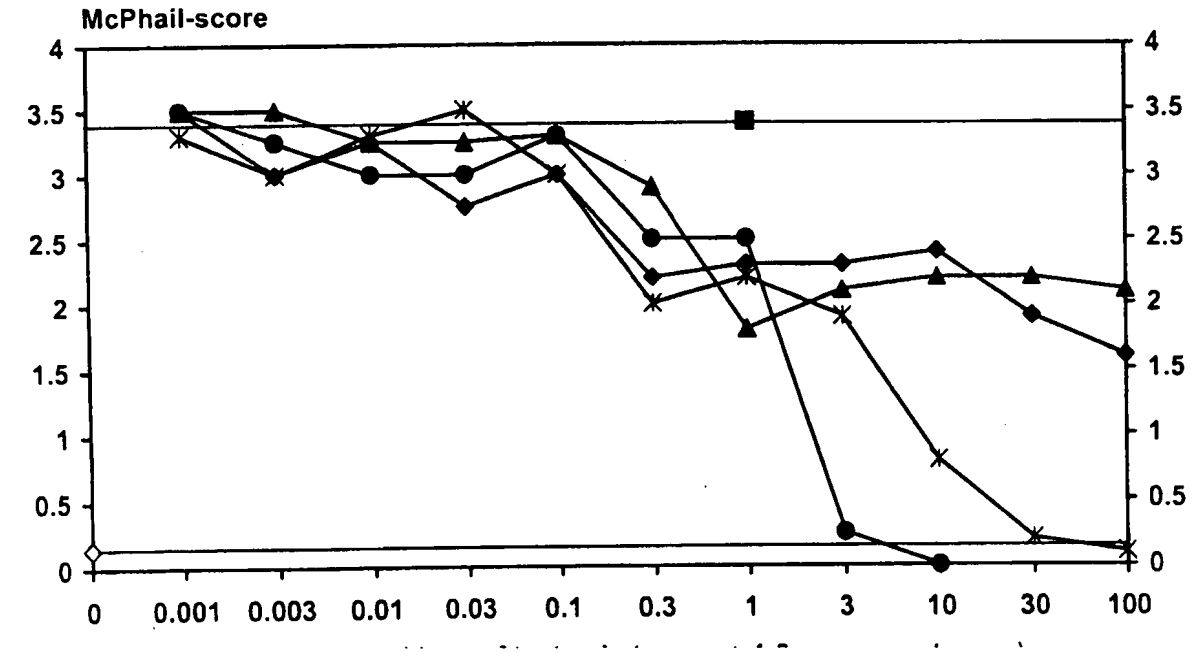


Figure 2

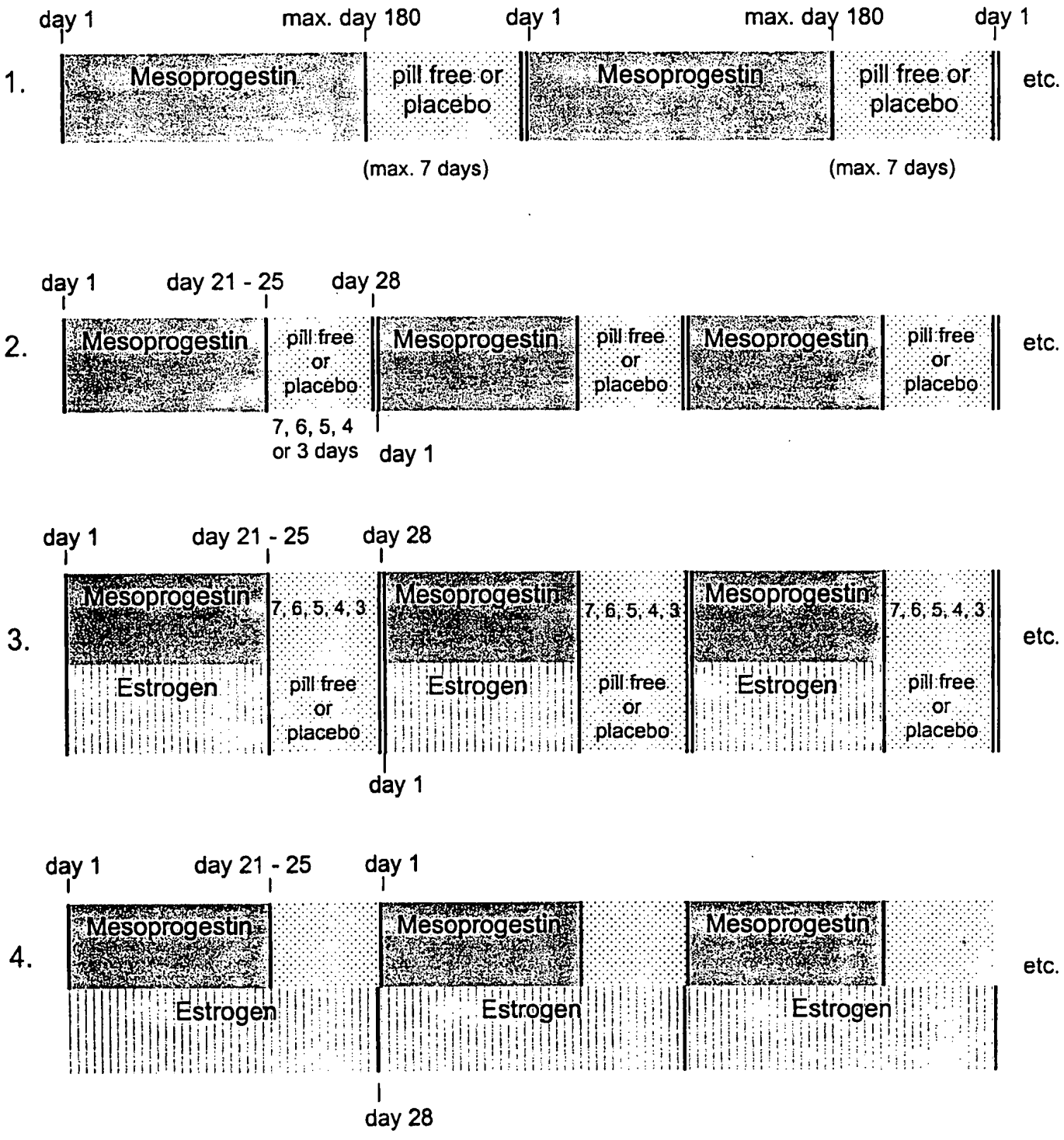
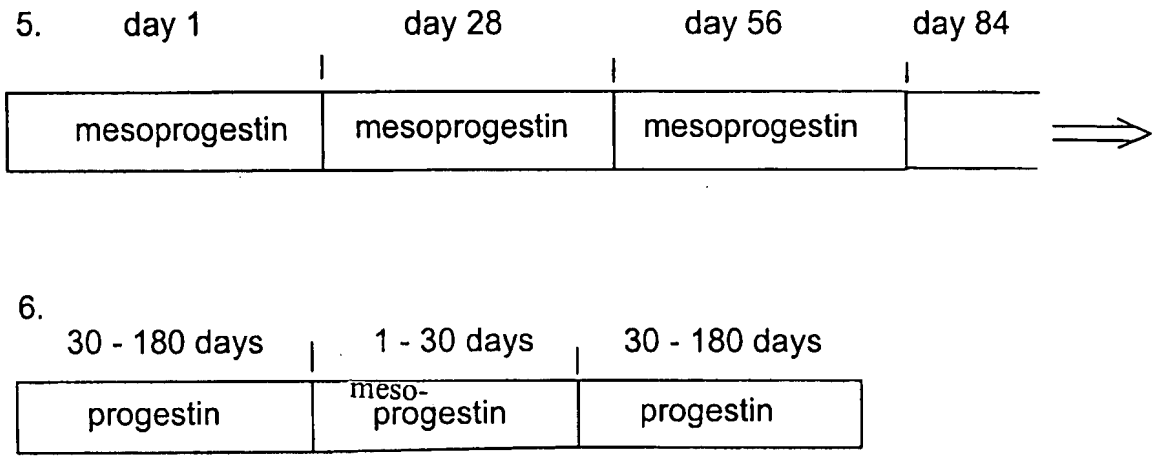
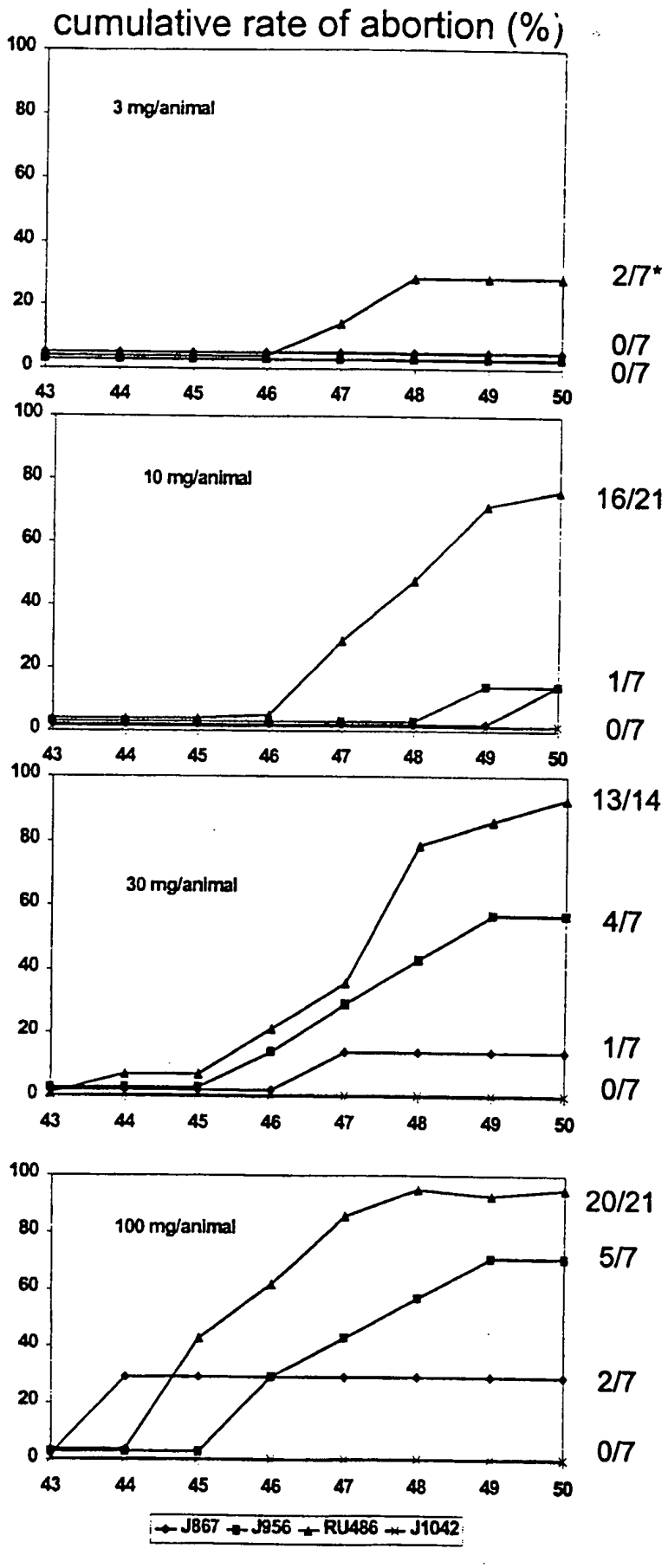

day 1
max. day 180
day 1
max. day 180
day 1
1.
Mesoprogestin
pill free or placebo
Mesoprogestin
pill free or placebo
etc.
(max. 7 days)
(max. 7 days)
day 1
day 21 - 25
day 28
2.
Mesoprogestin
pill free or placebo
Mesoprogestin
pill free or placebo
Mesoprogestin
pill free or placebo
etc.
7, 6, 5, 4 or 3 days
day 1
day 1
day 21 - 25
day 28
3.
Mesoprogestin
7, 6, 5, 4, 3
Estrogen
pill free or placebo
Mesoprogestin
7, 6, 5, 4, 3
Estrogen
pill free or placebo
Mesoprogestin
7, 6, 5, 4, 3
Estrogen
pill free or placebo
etc.
day 1
day 1
day 21 - 25
day 1
4.
Mesoprogestin
Estrogen
Mesoprogestin
Estrogen
Mesoprogestin
Estrogen
etc.
day 28

Fig. 2 (con't.)


5.
day 1
day 28
day 56
day 84
mesoprogestin
mesoprogestin
mesoprogestin
6.
30 - 180 days
1 - 30 days
30 - 180 days
progestin
meso-
progestin
progestin


cumulative rate of abortion (%)
3 mg/animal
2/7*
0/7
0/7
10 mg/animal
16/21
1/7
0/7
30 mg/animal
13/14
4/7
1/7
0/7
100 mg/animal
20/21
5/7
2/7
0/7
J867 J956 RU486 J1042